Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 171–175

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Relationship between hypothyroidism and the incidence of gestational diabetes: A meta-analysis

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ARTICLE INFO

Article history:
Accepted 16 January 2015

Keywords:
gestational diabetes
hypothyroidism
meta-analysis

ABSTRACT

Objectives: Hypothyroidism disorders and gestational diabetes are among the most common endocrinopathies during pregnancy. We conducted a meta-analysis to investigate whether hypothyroidism in pregnancy is associated with gestational diabetes risk.

Materials and methods: Published literature from PubMed and EMBASE were searched for eligible publications. Pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using a fixed- or random-effects model.

Results: Seven articles described the relationship between hypothyroidism and risk of gestational diabetes. This meta-analysis revealed that overt hypothyroidism was associated with an increased risk of gestational diabetes (OR 1.892, 95% CI 1.679–2.132, $p < 0.001$). The relative risk of gestational diabetes was also increased in subclinical hypothyroidism, with the OR of 1.558 (95% CI 1.292–1.877, $p < 0.001$). There was no evidence of significant association between hypothyroxinemia and risk of gestational diabetes (OR 1.394, 95% CI 0.753–2.580, $p = 0.291$). The OR for all of the hypothyroidism was 1.749 (95% CI 1.586–1.928, $p < 0.001$), and an association was found.

Conclusion: Results of this meta-analysis indicate that hypothyroidism may be a risk factor for gestational diabetes.

Introduction

Hypothyroidism is a condition in which the thyroid gland fails to produce a sufficient amount of thyroid hormone to meet the metabolic demands of the body. In laboratory testing, *overt hypothyroidism* is classified as an elevated level of serum thyrotropin-stimulating hormone (TSH) in combination with low thyroxine (T3) or triiodothyronine (T4) levels. *Subclinical hypothyroidism* is a biochemical diagnosis defined by a normal free T4 level and an elevated TSH level. *Isolated hypothyroxinemia* is characterized by a normal serum TSH and low serum FT4 levels.

Thyroid hormones exert profound effects in the regulation of glucose homeostasis, and hypothyroidism can have profound effects on glucose metabolism and insulin secretion. Pregnancy has a profound impact on the thyroid gland and its functioning. It is well-known that thyroid hormone requirements increase during pregnancy. During pregnancy the prevalence of overt and subclinical hypothyroidism is 0.5% and 2–3%, respectively [1,2]. Up to now, hypothyroidism has been thought to be associated with pregnancy complications such as gestational diabetes [3–7], but these relationships have not been proved in all studies [8,9]. Therefore, we performed a meta-analysis to find out whether hypothyroidism in pregnancy is associated with gestational diabetes risk.

Materials and methods

Literature search

We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [10] and Meta-analysis of Observational Studies in Epidemiology [11] guidelines. We searched the English biomedical literature via PubMed and EMBASE. We also evaluated other meta-analyses and references from related articles to identify relevant

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http://dx.doi.org/10.1016/j.tjog.2016.02.004

studies. The search strategy to identify all potential studies involved the use of combinations of the following keywords: ("hypothyroidism") AND ("Gestational Diabetes" OR "Gestational Diabetes Mellitus" OR "Pregnancy Induced Diabetes"). The data were last updated on September 2014.

Study selection and data extraction

The following criteria were set to choose the studies for this meta-analysis: (1) based on a case–control design or cohort studies; (2) evaluating the association of hypothyroidism and gestational diabetes; (3) data available for both cases and controls. Data were extracted independently by two authors (L.L.G. and H.L.). Any disagreement was resolved by discussion or through a third investigator and consensus. We extracted the following data from the selected articles: the first author's surname, publication year, country of origin, mean age and ethnicity, numbers of cases and controls.

Meta-analysis

The association between hypothyroidism and gestational diabetes was estimated by calculating odds ratios (ORs) and 95% confidence interval (CI). We estimated the risk of gestational diabetes in hypothyroidism and overt/subclinical hypothyroidism subgroups.

Statistical analysis

The association between hypothyroidism and gestational diabetes was estimated by calculating ORs and 95% CI. The random- or fixed-effects model [12] was used to calculate the pooled OR. Cochrane Q test, which was considered statistically significant with $p < 0.100$, was performed to evaluate the heterogeneity among studies [13]. I^2 statistic was used to quantify heterogeneity between studies ($I^2 < 25\%$, no heterogeneity; $I^2 = 25–50\%$, moderate heterogeneity; and $I^2 > 50\%$, extreme heterogeneity). Publication bias was assessed with a Begg's funnel plot [14] and Egger weighted regression method [15] for those analyses with greater than three trials ($p < 0.05$ indicated significant bias). The sensitivity analyses were performed to assess the stability of the results. The influence of individual studies was examined by omitting one study at a time to see the extent to which inferences depend on a particular study or a group of studies. Meta-analysis was performed using the STATA software system (version 11.0; Stata Corporation, College Station, TX, USA). Sensitivity analysis was performed by sequential removal (statistics of study remove) of individual studies (Review Manager 5.0 software).

Results

Search findings

Characteristics of studies investigating the relationship between hypothyroidism and gestational diabetes are presented in Table 1. After excluding the duplicate articles and irrelevant articles, seven studies met our inclusion criteria for the meta-analysis. Among the articles that were included in this meta-analysis, six investigated the effect of subclinical hypothyroidism on the susceptibility of gestational diabetes: three studies involved overt hypothyroidism and gestational diabetes and three studies on the relationship between hypothyroxinemia and gestational diabetes.

Hypothyroidism and risk of gestational diabetes

This meta-analysis revealed that overt hypothyroidism was associated with an increased risk of gestational diabetes (OR 1.892, 95% CI 1.679–2.132, $p < 0.001$; Figure 1). The relative risk of gestational diabetes was also increased in subclinical hypothyroidism, with the OR of 1.558 (95% CI 1.292–1.877, $p < 0.001$; Figure 2). There was no evidence for significant association between hypothyroxinemia and risk of gestational diabetes (OR 1.394, 95% CI 0.753–2.580, $p = 0.291$). The OR for all of the hypothyroidism was 1.749 (95% CI 1.586–1.928, $p < 0.001$; Figure 3), and an association was found. Summary of results from our meta-analysis evaluating the association between hypothyroidism and risk of gestational diabetes is presented in Table 2.

Sensitivity analysis

To compare the difference and evaluate the sensitivity of the meta-analyses, we conducted a sensitivity analysis to evaluate the stability of the meta-analysis. The statistical significance of the results was not altered in any of the analysis when any single study was omitted, confirming the stability of the results.

Publication bias

We used Begg's funnel plot and Egger's test to access the publication bias in the literature search. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Figure 4). No publication bias could be detected for the association between overt hypothyroidism, subclinical hypothyroidism, hypothyroxinemia, and the incidence of gestational diabetes (Table 2).

Table 1
Characteristics of studies about hypothyroidism and gestational diabetes included in the meta-analysis.

Author [Reference]	Year	Country	Cases			Controls	
			Subgroup	Total	Gestational diabetes	Total	Gestational diabetes
Casey et al [7]	2007	USA	Subclinical hypothyroidism	598	55	16,011	850
			Hypothyroxinemia	233	10		
Cleary-Goldman et al [8]	2008	UK	Subclinical hypothyroidism	240	6	10,021	301
			Hypothyroxinemia	232	14		
Mannisto et al [9]	2010	Finland	Overt hypothyroidism	54	4	4708	61
			Subclinical hypothyroidism	222	6		
			Hypothyroxinemia	227	5		
Sahu et al [3]	2010	India	Clinical hypothyroidism	29	1	552	18
			Subclinical hypothyroidism	41	0		
Tudela et al [4]	2012	USA	Subclinical hypothyroidism	528	35	23,771	998
Mannisto et al [6]	2013	USA	Primary hypothyroidism	3183	298	21,6901	10,805
			Iatrogenic hypothyroidism	178	14		
Nelson et al [5]	2014	USA	Subclinical hypothyroidism	230	24	6645	417

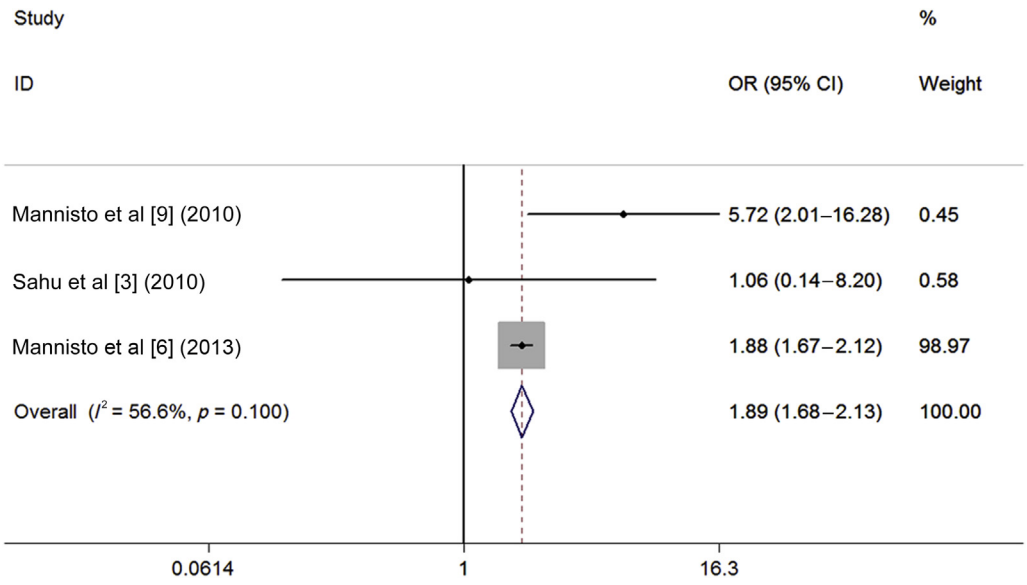

Figure 1. Odds ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for the association between overt hypothyroidism and incidence of gestational diabetes.

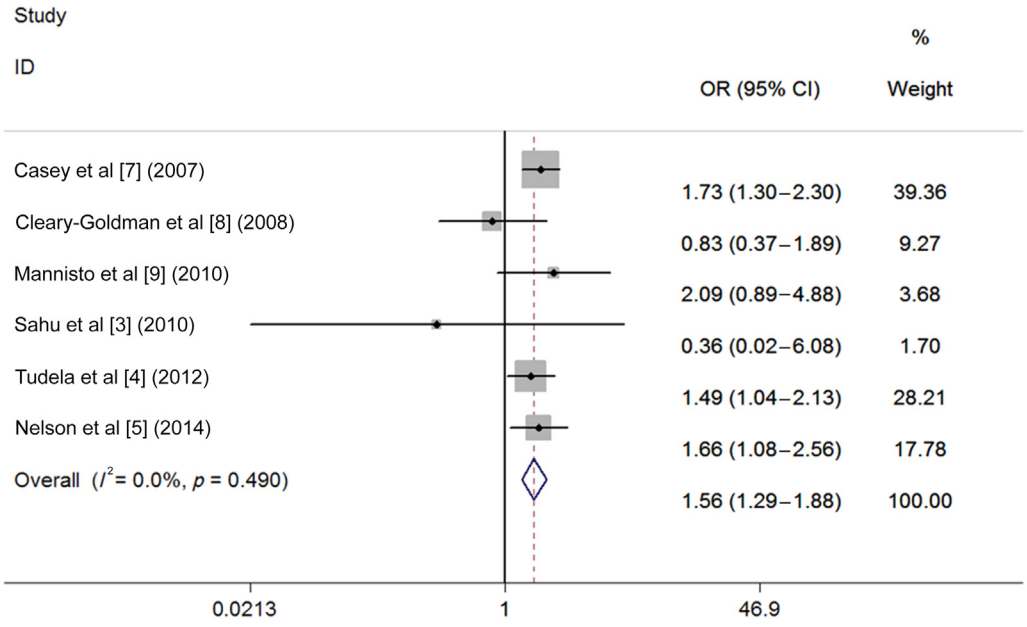

Figure 2. Odds ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for the association between subclinical hypothyroidism and risk of gestational diabetes.

Discussion

Hypothyroidism disorders and gestational diabetes are among the most common endocrinopathies during pregnancy. Many studies have evaluated the association between hypothyroidism and gestational diabetes risk. While some reports found such an association, others failed to demonstrate this connection, and the results are often conflicting. Identifying the relationship between hypothyroidism and gestational diabetes could help with early diagnosis and treatment of these disorders.

Hypothyroidism appeared to negatively affect glucose homeostasis by inducing insulin resistance. Pregnant women with hypothyroidism have further amplified insulin resistance, and thus have an increased risk of gestational diabetes. In this study, women with overt hypothyroidism were at a significantly greater risk of gestational diabetes when compared with euthyroid women. Women with subclinical hyperthyroidism also had a significantly higher risk of developing gestational diabetes when compared with euthyroid women. Hypothyroxinemia was not associated with the risk of gestational diabetes.

Several potential limitations of this study should be considered. As only seven studies were included in this meta-analysis, these results should be interpreted with caution. Further functional studies are required to investigate the association between hypothyroidism and the incidence of gestational diabetes. We could not exclude the possibility of publication bias for some comparisons

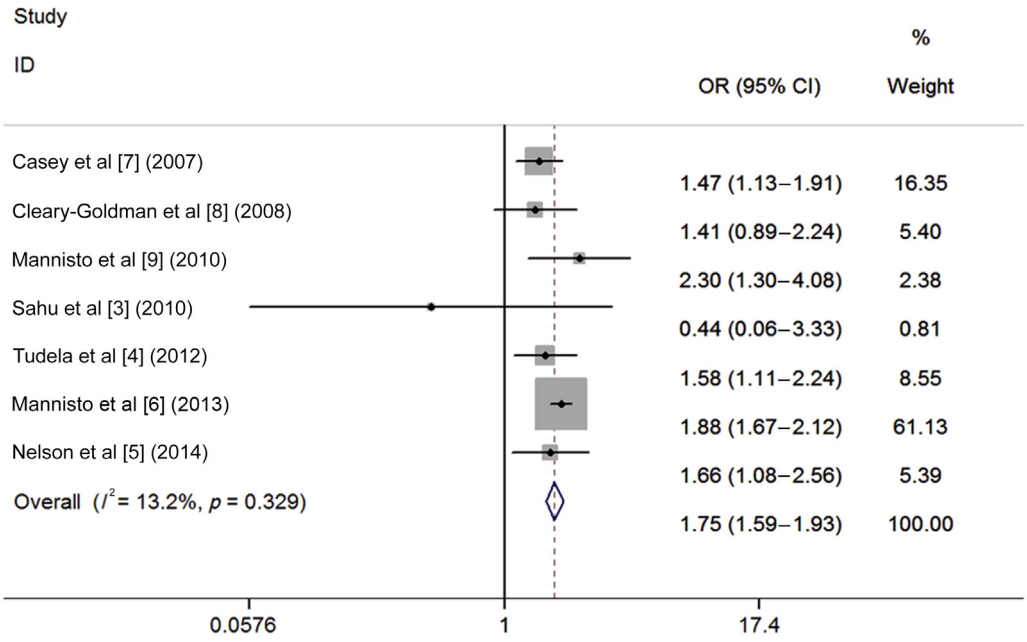

Figure 3. Odds ratio (OR) and 95% confidence interval (CI) of individual studies and pooled data for the association between all of the hypothyroidism and risk of gestational diabetes.

Table 2
Summary results of various comparisons.

Subgroup	OR (95% CI)	*p*-Heterogeneity	*p*	*p*-Publication bias
All	1.749 (1.586–1.928)	0.329	<0.001	0.140
Overt hypothyroidism	1.892 (1.679–2.132)	0.100	<0.001	0.688
Subclinical hypothyroidism	1.558 (1.292–1.877)	0.490	<0.001	0.205
Hypothyroxinemia	1.394 (0.753–2.580)	0.089	0.291	0.939

CI = confidence interval; OR = odds ratio.

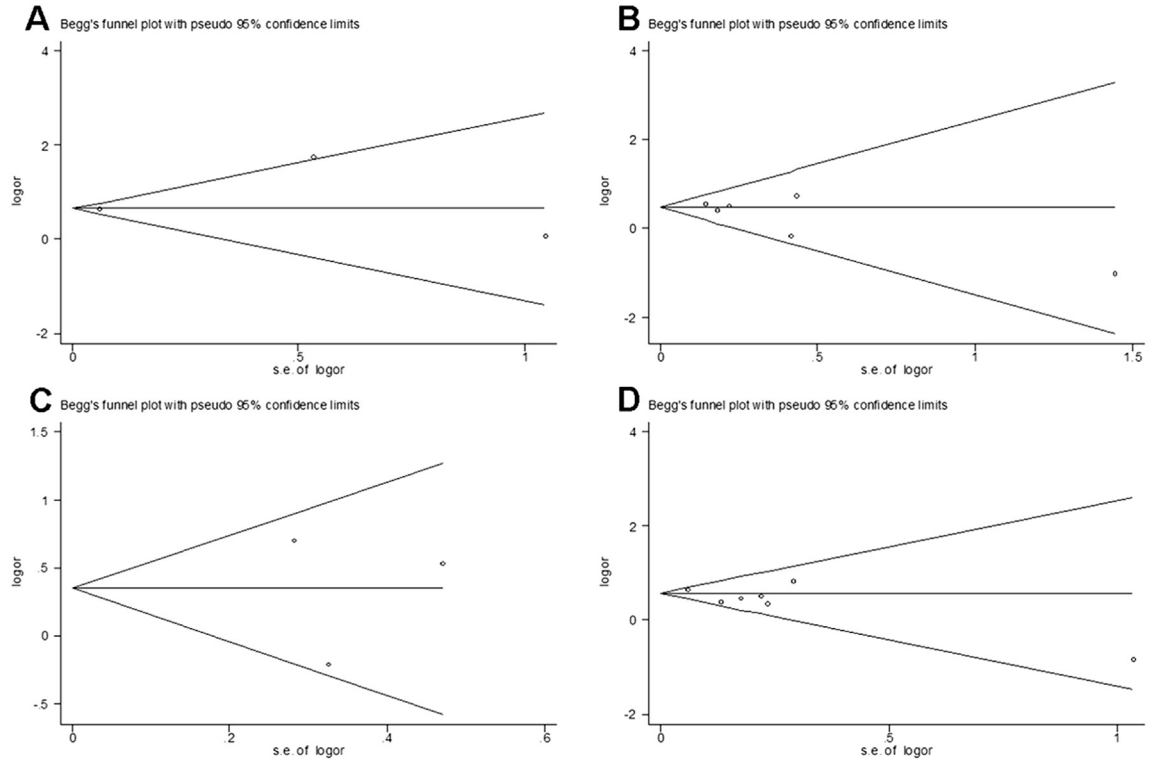

Figure 4. Begg's funnel plot analysis to detect potential publication bias: (A) overt hypothyroidism; (B) subclinical hypothyroidism; (C) hypothyroxinemia; (D) all of the hypothyroidism. s.e. = standard error.

and outcomes, because some negative and unexpected results may not be published. Therefore, the results of our meta-analysis should be interpreted with caution.

In conclusion, a total of seven publications containing 5995 cases and 278,609 controls were selected in the study. Our results indicate significant associations between hypothyroidism and the risk of gestational diabetes. These findings would suggest that routine assay of thyroid hormones during pregnancy could be warranted. More studies with larger sample size and multiple subgroups are needed to further explore the association between them.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (Grant No. 81302822).

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